THE EFFECT OF

THEOPHYLLINE-ETHYLENEDIAMINE

IN

CHEYNE-STOKES RESPIRATION.

by

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Localisation of the respiratory centre:- The respiratory centre, which is constituted by the integration of many neurons, has been localised in a relatively extensive area between the upper border of the pons and the lower third or so of the medulla oblongata. It has been demonstrated by V. E. Henderson and Craigie, by Gesell, Bricker and Magee that these neurons are scattered at different levels through the formatio reticularis of these parts of the brain stem. The centre is bilateral and each half contains inspiratory and expiratory components that control muscles of inspiration and expiration respectively.

The nervous structures controlling respiration has been localised by Markwald. The fact that powerful and prolonged tonic inspiratory movements supervened after bilateral section of the vagus nerves and division of the brain stem immediately behind the posterior colliculi, made him conclude that a centre inhibitory to respiration was located in the posterior colliculi.

The vagi however also has an inhibitory action, consequently these inspiratory movements, or "cramps", as he termed them, appeared only after their influence had been abolished as well. In recent years Lumsden found that prolonged inspiratory movements occurred only if the section passed through the pons a few millimetres behind its anterior border, and occurred whether the vagi were divided or not, and that these respiratory movements were dependent upon an apneustic or inspiratory centre situated at the level of the striae accousticae, which was dominated normally by an inhibitory or pneumotoxic centre situated in the upper part of the pons. On account of the inhibitory influence of the latter, the apneustic movements were transformed into the rhythmical movements characteristic of normal respiration, as shown by the fact that rythmic action currents are registered by leads from the medulla. Section of the brain stem behind the striae accousticae brought about a series of gasps occurring at relatively long intervals.

It was demonstrated by Pitts, Magoun and Ranson that so long as the vagi were intact, animals decerebrated through the upper part of the pons maintained a normal type of respiration which responded in the usual way to peripheral nerve stimulation;

when however the vagi were severed, apneustic respirations and a complete cessation of rhythmical movements immediately developed. The apneustic centre is therefore under a double inhibitory influence, either of which is capable of converting the apneustic type of respiration to the normal or nearly normal rhythm of respiration. The stretch of the lung towards the latter part of the inspiratory phase of normal breathing initiate the vagal impulses which influence the apneustic centre.

As in normal inspirations, the carbon dioxide tension of the blood has a powerful effect on the apneuses, increasing the depth if a high concentration of carbon dioxide in the air is breathed, and reducing the depth or preventing it from occurring when there is a carbon dioxide lack.

In 1868 it was pointed out by Hering and Breuer that inflation of the lungs arrested inspiration, expiration then ensuing, while deflation of the lungs inhibited expiration, bringing on inspiration. These are reflex effects, mediated through afferent fibres of the pulmonary vagi, for, after these nerves have been divided, an abolition of these effects follows. In ordinary breathing, only the inflation reflex comes into play, as further distension of the lungs is checked at the end of an

inspiration of the usual duration.

That the aortic area can give rise to respiratory reflexes was discovered in 1927 by Heymans and Heymans. They found that in each of the carotid and aortic areas there is present a pressoreceptor, which respond to chemical stimulation. The pressoreceptors situated among the collagenous fibres in the wall of the carotid sinus and in the wall of the aortic arch are stimulated by a stretching force, as by a rise in arterial blood pressure. The chemoreceptors on the other hand are contained in small glandular structures, the carotid and aortic bodies. The respiratory reflexes initiated from these two types of receptors are contrary in their effects. It was demonstrated that stimulation of the pressoreceptors inhibited respiration, such as follows the abrupt rise of blood pressure after the injection of adrenalin. Excitation of the chemoreceptors however, increased the depth and rate of breathing. If the supplying nerves were severed, both types of the reflexes were abolished.

Oxygen lack stimulates the chemoreceptors, but this occurs only after the oxygen tension of the arterial blood has reached a relatively low level. The chemoreceptors are even less sensitive to carbon dioxide, as shown by the isolation of the

carotid body from the general blood stream, keeping the nerve supply however intact and perfusing it with a solution containing carbon dioxide. Denervation of the carotid area induces hyperpnoea after a change of only 3 millimetres mercury in the blood supplying the respiratory centre. It appears therefore that the chemoreceptors, being relatively insensitive to a reduction in oxygen or a rise in carbon dioxide tension, play hardly any role in ordinary physiological conditions.

The reflex response of the chemoreceptors, especially to anoxia, is of the highest importance in more exacting emergencies. As a stimulus to the respiratory centre anoxia seems to be ineffective. Depression and ultimate failure of the central neurons is the predominant effect of oxygen lack. The chemoreflex mechanism on the other hand, is highly resistant to anoxia, as it retains its viability and continues to exert its influence upon the centre which otherwise would be unresponsive in the emergencies of the body.

Any condition apparently which alters the relationship between their oxygen supply and the metabolic need at the time seems to stimulate the chemoreceptors. It is thought that the immediate

stimuli are the acid products of their own metabolism. Thus not only anoxia, but poisoning the cells with cyanide or sulphide, ischemia of the carotid body, or increasing its metabolism as by application of heat, are all capable of eliciting a hyperpnoeic reflex.

Reflexes are also initiated in other parts of the body, as shown by the fact that stimulation of almost any afferent nerve may bring about a reflex change in respiration, as for example stimulation of the pain fibres; effects of extreme heat and cold; muscular exercise; propioceptive impulses from the diaphragm and other respiratory muscles during one respiratory phase exert an important influence upon the succeeding movement.

Chemical stimulation of the respiratory centre:- The action of carbon dioxide on the respiratory centre is responsible for the chemical control of respiration under ordinary physiological conditions. It was demonstrated by Haldane and Priestley that in a man the pulmonary ventilation was doubled by only 0.2 per cent rise in the carbon dioxide of the alveolar air. The question arises as to whether the stimulation of the respiratory centre by carbon dioxide is simply due to the raising

of the H ion concentration of the nerve cells composing the centre, due to the easier penetration of carbon dioxide into their interiors? That carbon dioxide acts specifically upon the respiratory centre has been shown by Krogh and his associates, who found that in human subjects the extreme hyperpnoea following the inhalation of carbon dioxide, only resulted in very little change in the arterial pH. The ingestion of ammonium chloride on the contrary, while lowering the pH of the arterial blood to a marked degree, caused hardly any or no increase in breathing.

While the condition of hyperpnoea can be brought about by the inhalation of carbon dioxide, it can readily be produced by impulses reaching the respiratory centre from the cerebral cortex, as for example in excitement and emotional states; by stimulation of the sensory nerves, for example heat and cold to the skin and by muscular exercises.

After overventilation of the lungs for a minute or two by stimulation of the sensory nerve, inducing hyperpnoea, the condition of apnoea results. This can also be brought about by sending inhibitory impulses to the respiratory centre, for example

by stimulating the central end of the vagus, or by distending the lungs. The apnoea that follows over breathing is brought about by excessive elimination of carbon dioxide and in consequence a lowering of the tension of this gas in the blood.

Periodic Breathing:- This type of breathing includes various types of uneven respiratory rhythm. It was described by Hippocrates as follows: "The breathing throughout was rare and large, as though he were recollecting to do it." The most common type of periodic breathing and one which takes on a regular periodic form is known as Cheyne-Stokes respiration. It was first observed by Dr. Cheyne, of Dublin, in 1818; and summarised by Stokes, a contemporary of Cheyne as follows: "For several days his breathing was irregular; it would entirely cease for a quarter of a minute, then it would become perceptable, though very low, then by degrees it became heaving and quick, and then it would gradually cease again. This revolution in the state of his breathing occupied about a minute, during which there were about thirty acts of respiration".

It appears however, that this phenomenon of periodic breathing was observed by John Hunter and Nicholas, a physician of Grenoble, as far back as 1786, where he describes the respiration of an officer of 81 years: " But what indeed

more extraordinary than this irregularity (of pulse) was an absolute suspension, a cessation of the movements of the lung for twenty five to thirty seconds at each thirty-fifth or thirty-sixth respiration then the play of the organ was re-established little by little, and by a very evident gradation it resumed its ordinary energy to stop again almost at an indicated instant."

Cheyne-Stokes breathing is therefore defined "as a form of involuntary periodic breathing in which periods of apnoea alternate with periods of respiration waxing to hyperpnoea or even dyspnoea, then waning again to apnoea, which may last for a minute or more." The hyperpnoeic and apnoeic phases last each for about thirty seconds. Periodic breathing of this type occurs at high altitudes and has been observed also in healthy infants and occasionally in normal adults during sleep. The most common clinical conditions in which Cheyne-Stokes respiration has been observed are advanced cardiac and renal diseases, resulting frequently in great subjective distress and interfering with the patient's rest and sleep. It thus becomes a definite factor in preventing improvement of the cardiac state. In more extensive cases periodic breathing becomes continuous and the patient is constantly disturbed by the

repeated cycles of deep breathing. The most common cause is cardiac arteriosclerosis, and especially if this is associated with hypertension, cerebral arteriosclerosis and uremia. It appears further that Cheyne-Stokes respiration is more common in cases involving the left ventricle and in hypertensive and aortic diseases than in circulatory failure secondary to initial stenosis or pulmonary disease.

Apart from circulatory disturbances Cheyne-Stokes respiration appears sometimes in asthma, lobar pneumonia and frequently in cases of raised intracranial pressure, for example, meningitis, brain tumours, cerebral haemorrhages, and sometimes in the terminal stages of acute infections. It is also seen in morphine and chloral poisoning, or it may follow a general anaesthetic. It may occur, though rarely, after forced breathing. It was induced experimentally by Douglas and Haldane in normal persons by a moderate degree of oxygen want. Clinical Cheyne-Stokes respiration is generally regarded as a grave sign, and is probably the result in most cases, of damage to the respiratory centre caused by oxygen lack, which may be the result of defective aeration of the blood in the lungs, or of slowing of the circulation through the medulla,

as in cases of circulatory failure or increased intracranial pressure. In many cases, the Cheyne-Stokes respiration can be abolished by the administration of oxygen, but in others again, oxygen does not alter the periodicity to any degree. What probably happens is that the depressed state of the respiratory centre results in quick shallow breathing, which increases the anoxia. The oxygen lack stimulates the respirations, and according to Douglas and Haldane also increases the sensitivity of the centre to carbon dioxide. The respirations increase in vigour, but as the carbon dioxide is eliminated, they subside again. During the period of breathing however, the carbon dioxide tension of the blood flow is reduced to a level below that at which the centre is stimulated and apnoea results. During this apnoeic period, the increasing oxygen want raises the irritability of the centre, and the accumulating carbon dioxide in the arterial blood stimulates the respiratory centre and breathing returns. For a while the carbon dioxide tension is relatively high, and the respirations are deep and vigorous. This results in an increase in the oxygen saturation of the blood, a reduction in the carbon dioxide tension, the centre is no longer excited and apnoea recurs.

Gesell believes that the chemoreceptors which reflexly induce the augmented respirations, are excited by the anoxemia occurring during apnoea. The carbon dioxide is blown off by the greater ventilation and the resulting depression of the respiratory centre causes apnoea.

It was pointed out by Douglas and Haldane that the elimination of large quantities carbon dioxide from the body during the hyperpnoeic periods and the ultimate reduction of the bicarbonate reserve, removes a steadying influence which is normally exerted upon the respiratory centre. A large store of carbon dioxide is held in the lungs and also in the tissue fluids as bicarbonate, and upon this is drawn to oppose a sudden fall in the carbon dioxide tension of the blood supplying the respiratory centre. The excess carbon dioxide, however, is buffered by the tissue fluids, and this prevents any sharp rise in the carbon dioxide tension. The reduction of the bicarbonate reserve in Cheyne-Stokes respiration allows slight changes in the gas tensions to produce sudden and exaggerated fluctuations in the activity of the centre. The administration of carbon dioxide, as shown by Allen and Pembury, abolishes in many instances the periodic rhythm.

In cases of increased intracranial pressure, periodic breathing has been found to be due to an alternating elevation and depression of the blood pressure where the hyperpnoeic phase coincides with the blood pressure rise. In these cases the immediate cause of the respiratory rhythm may be the change in blood pressure. On the other hand, a fall in arterial pressure below intracranial pressure, by causing an acute anaemia of the centre, would suppress its activity for the time and induce apnoea, which would give place to hyperpnoea as soon as the arterial pressure is raised, when the vessels of the centre are again filled.

From clinical observations one must conclude that oxygen deficiency per se does not suffice to cause Cheyne-Stokes breathing, for patients with congenital heart disease and cyanotic for years rarely develop periodic breathing, as also cases with right ventricular failure secondary to pulmonary lesions. It therefore appears that only under certain conditions and in association with other factors Cheyne-Stokes respiration is produced. Often too, there is clinical evidence that quite a number of the factors mentioned, function in the production of

Cheyne-Stokes respiration in an individual case.

<u>Abolition of Cheyne-Stokes Respirations</u>:-

As a means of abolishing Cheyne-Stokes respirations and the accompanying subjective discomfort use has been made of theophylline-ethylenediamine. Its use was first described by Vogl in 1927, but as to its mode of action there is still some doubt and an attempt has been made to elucidate this problem.

Theophylline-ethylenediamine was first introduced by Grüter in 1910, as the result of a search for a water soluble xanthine diuretic for administration other than orally. In 1908 Grüter found a substance highly soluble in water, produced from the interaction of ethylenediamine or more other important aliphatic amines on theophylline. Out of these theophylline compounds theophylline-ethylenediamine was chosen, because it proved theoretically and practically the best. Theophylline-ethylenediamine is a combination of one molecule of theophylline with ethylenediamine:-

$$\begin{matrix} CH_2\ NH_2 \\ | \\ CH_2\ NH_2 \end{matrix} \longleftarrow C_7H_8N_4O_2$$

Ethylenediamine Theophylline

Theophylline itself is very insoluble, and even the double salt of theophylline with sodium acetate

is only soluble in 25 parts of water. Theophylline-ethylenediamine however, is quite soluble and easily forms a 40 per cent. solution. Ethylenediamine was the simplest representative of the aliphatic diamine and its somewhat higher homologues Tetra- and Penta-methylenediamine, typical physiological products, and it was used at first because of its non toxity, but it was soon found that the compound had pharmacological properties not found in other forms of theophylline.

Theophylline-ethylenediamine was also introduced under the trade name of Euphyllin, which was highly water soluble, giving easily a 40 per cent. solution, and it contained about 78 per cent. theophylline and 20 per cent. ethylenediamine. This preparation Euphyllin was used throughout this investigation.

Vogl (1932), in summarising five years' experience with euphyllin in Cheyne-Stokes respiration, states that it never fails to restore the respiration to a normal type. He found the action to be most pronounced in cases of cardiac insufficiency, but sometimes transient, especially when periodic breathing results from head injuries or intracranial haemorrhage.

The following cases illustrate the action of euphyllin or one of its component parts. The terms "Cheyne-Stokes" breathing and "periodic" breathing

have been regarded as synonymous, although the latter term has been used particularly to include regular periodic waxing and waning of respiration without the true apnoeic pauses emphasised in the original descriptions of Cheyne and Stokes.

CASE 1: Syphilitic aortitis and atheroma. A retired ship's fireman, aged 68, complaining of periodic breathlessness, and giving a history of precordial pain a month previously. There was no oedema or general venous congestion, but a good deal of bronchitis and pulmonary congestion. The heart was hypertrophied and a double aortic murmur was audible. The Wassermann reaction was strongly positive, and radiography revealed diffuse dilatation of the aortic arch with calcification. Electrocardiograms showed evidence of recent coronary thrombosis. Cheyne-Stokes breathing was pronounced, but became less obvious after rest in bed for a few weeks when the bronchitis and pulmonary congestion had subsided.

A single intravenous injection of 0.36 gramme euphyllin abolished completely the Cheyne-Stokes respiration during the course of a slow injection (Fig. 1). The effect of euphyllin was maintained for many hours, and when Cheyne-Stokes re-

spiration ultimately again developed, theobromine sodium acetate (0.6 g.) and also theophylline sodium acetate (0.6 g.) was given intravenously in an attempt to find another drug with the same effect. These however, failed to abolish the Cheyne-Stokes respiration (Figs. 2 and 3). The latter injection was thereupon followed by one of the components of euphyllin, viz. ethylene-diamine (0.1 g.) intravenously, and again the Cheyne-Stokes respiration disappeared (Fig.3).

The effect of euphyllin in this patient was maintained often as long as sixteen hours after a single dose of 0.48 g.

CASE 2: Hypertensive heart failure. An engineman, aged 53, complaining of breathlessness on exertion. The blood pressure was 170/100, and he presented the usual features of severe heart failure with congestion, i.e. oedema of the legs and back, ascites, enlargement of the liver, pulmonary congestion, and oedema. The patient failed to show any maintained improvement with a succession of therepeutic measures, including digitalis, salyrgan and other diuretics, salt free diet, and Southey's tubes, and gradually the orthopnoea became more conspicuous and was accompanied by Cheyne-Stokes respiration. Sleep

was definitely disturbed by the periodic hyperpnoea, the onset of deep breaths waking him as he was dosing off to sleep.

Euphyllin 0.36 g. was administered intravenously and a stethograph record showed the abolition of Cheyne-Stokes respiration as the injection proceeded (Fig.4). This injection was given in the afternoon and that night the patient fell asleep without any sedatives, which were always needed on previous occasions. Three days later 0.16 g. ethylenediamine was given intravenously. This abolished the apnoeic phases, but periodic increases and decreases of respiration still persisted. The subsequent injection of 0.6 g. theophylline intravenously completed the restoration of the respiratory rhythm to normal. After another three days 0.6 g. theophylline intravenously was administered without effect and only a transient abolition of the Cheyne-Stokes respiration was achieved by 0.16 g. ethylenediamine which was given a few minutes later. A week after the first injection, 0.48 g. euphyllin intravenously abolished the Cheyne-Stokes respiration completely for two hours.

CASE 3: Chronic bronchitis and hypertensive heart failure. -- An unemployed miner aged 53. Cough, headaches, and breathlessness troubled

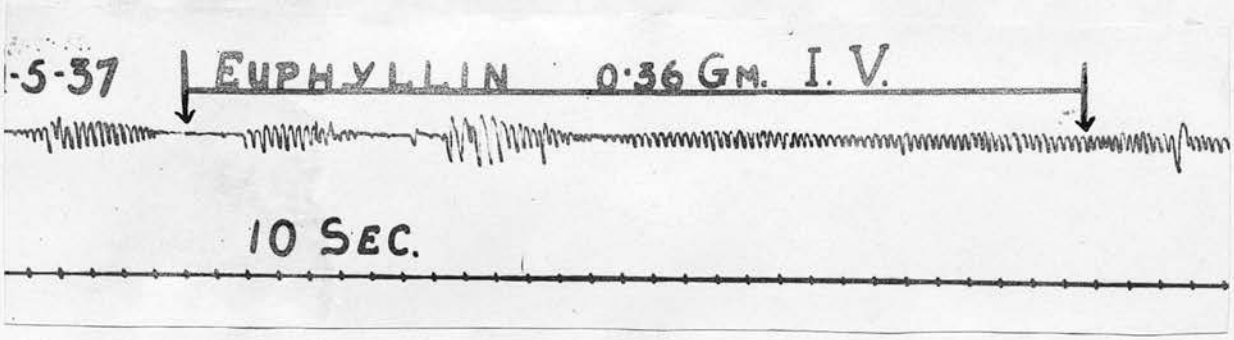

Fig. 1. The order of effects of intravenous injection of euphyllin is clearly shown: (1) increased depth of respiration in the hyperpnoeic phase; (2) shortening of the apnoeic pause; (3) diminution of periodicity leading on to completely normal respiration.

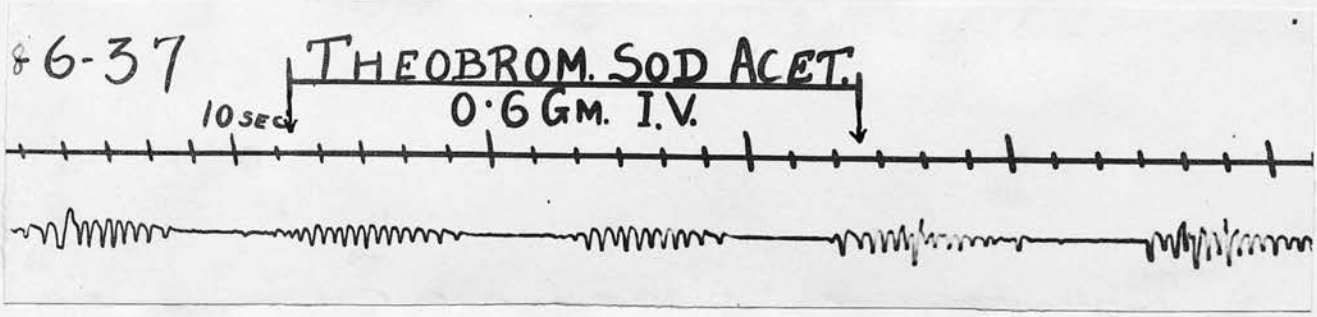

Fig. 2. Complete absence of any change in Cheyne-Stokes respiration after an intravenous injection of theobromine sodium acetate.

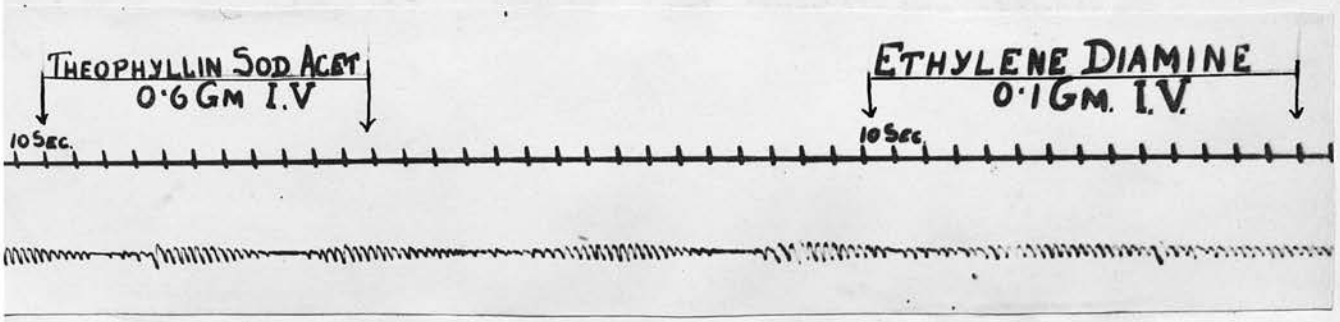

Fig. 3. Theophyllin sodium acetate alone is devoid of action, which is produced, however, by ethylenediamine.

him for five years. For six months he has had attacks of breathlessness which come on as he was falling asleep. These waken him and he fights for breath till the attack passes off. There was oedema of the legs; blood pressure 170/100; heart enlarged but no murmurs were present; rhonci and crepitations were heard all over both lungs, the latter most marked at the bases. The blood urea was 32 mg. per 100 c.cm.

He developed a pronounced degree of Cheyne-Stokes breathing. It was abolished by 0.60 g. euphyllin intravenously, but returned ten minutes after the injection. The action in this case was transient and the patient was not aware of any subjective improvement.

CASE 4: Rheumatic heart disease. -- A teacher aged 49 years. He gave a history of severe rheumatic fever when aged 11, but in spite of known cardiac damage, he was capable of considerable exercise including Alpine climbing. For eight years he has been incapable of such severe exercise, and has become increasingly breathless. Five months before admission to hospital he had influenza and since then he has been orthopnoeic. The patient showed slight oedema of the ankles, enlargement of the liver, a tinge of

jaundice, and engorgement of the veins of the neck up to the angle of the jaw. His blood pressure was 128/60. The heart was grossly enlarged, with systolic and diastolic murmurs at the aortic and mitral areas. The lungs showed oedema at the extreme bases. The patient had pronounced periodic waxing and waning of respiration; he often had attacks of severe breathlessness, particularly at night, which made sleep impossible without morphine.

An intravenous injection of 0.48 g. euphyllin was given, resulting in the abolition of the periodic respiration (Fig.5).

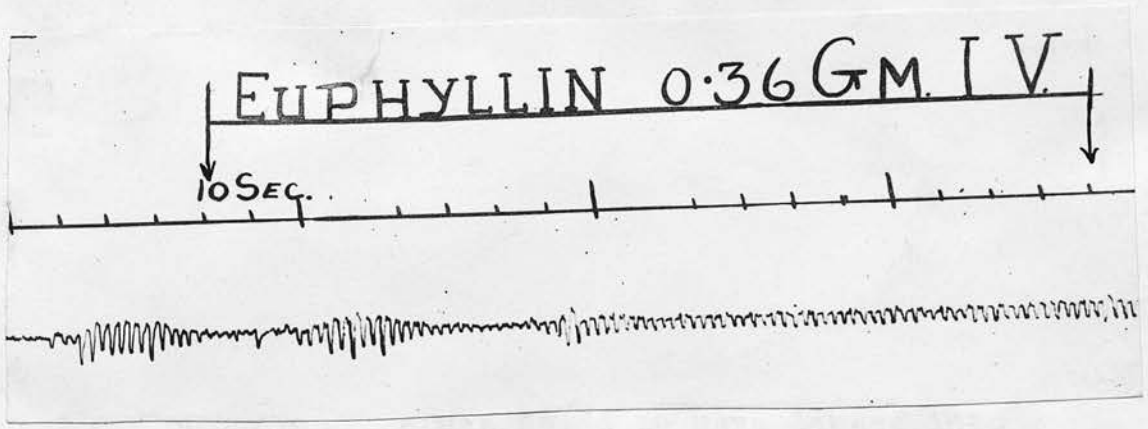

Fig. 4. Abolition of Cheyne-Stokes breathing by the intravenous injection of euphyllin.

At the same time the patient stated that he could see better, that his mind became clearer and that his breathing became easier and perfectly steady. In his own words, "the difference in breathing was almost unbelievable." That night he had a long undisturbed sleep without a sedative.

A respiratory record was taken to show the effect of the two components of euphyllin. An injection of 0.1 g. ethylenediamine was administered intravenously taking a shorter time for the injection than was the case previously. His respiration suddenly became very deep and rapid, with much subjective distress and anxiety. This patient regarded this condition as similar to the nocturnal attacks of dyspnoea which woke him up so frequently. After about two minutes the hyperpnoea subsided, but there was no apnoeic pause, the respiration continuing in a steady regular fashion, with complete disappearance of periodicity. A few minutes later 0.6 g. theophylline sodium acetate was given intravenously with no obvious additional change (Fig. 6). After a quarter of an hour he was found to have lapsed into periodic respiration once again. A further injection of 0.48 g. euphyllin was given, and again there was as on the previous occasion immediate subjective improvement and abolition of the periodic respiration.

That night, four hours after the last injection, a stethograph record of the respiration showed no periodicity whatsoever. He had an excellent sleep for seven hours, and was even able to lie flat. Twenty-two hours after the injection the respiration was still regular, but twenty-four hours after the injection the periodic breathing had returned.

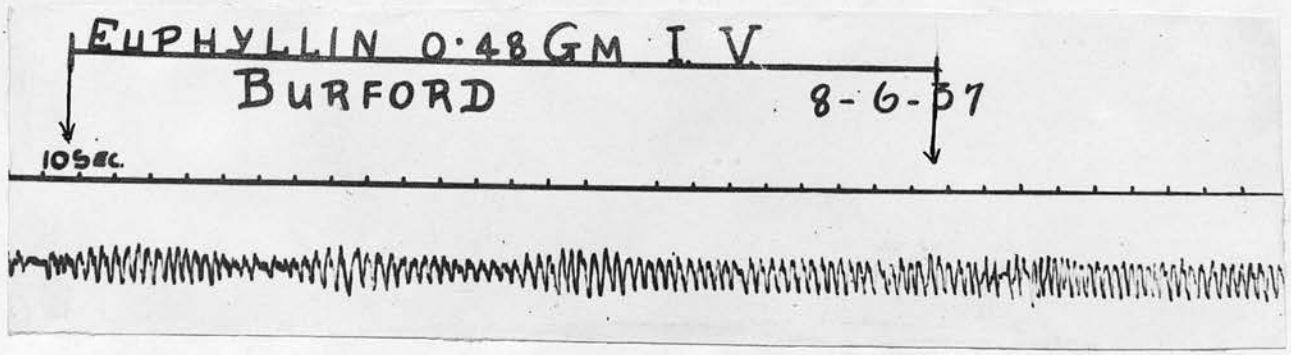

Fig. 5 Abolition of Cheyne-Stokes by euphyllin.

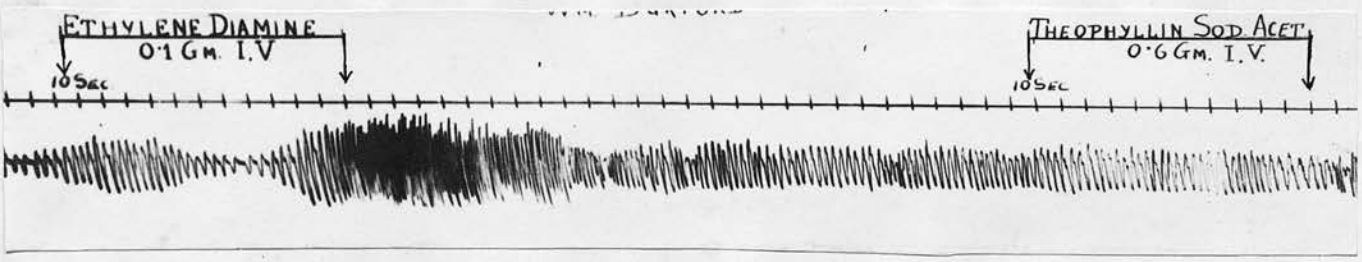

Fig. 6. Effect of 0.1 g. ethylenediamine. A great increase in rate and depth of respiration takes place followed by restoration to normal respiratory rhythm. No further action is produced by theophyllin sodium acetate.

CASE 5: Chronic bronchitis with cardiac enlargement. A Clerk aged 62 years. He had a very troublesome cough, the attacks lasting sometimes almost an hour. This was accompanied by marked breathlessness. For eight months he had attacks of nocturnal dyspnoea, and these had become so severe that he was unable to procure any sleep. There was no oedema of the legs; blood pressure 176/118; his heart was enlarged; no murmurs; rhonci and crepitations with prolongation of the expiratory sound all over both lungs. The rhonci and crepitations were most marked at the bases. The breathing showed a definite periodicity, more pronounced during sleep.

In the evening an intravenous injection of 0.48 g. euphyllin was given. The periodicity was abolished and the patient was able to procure a fairly restful six hours sleep without any other medicament, where morphine was mostly necessary. His breathing felt easier and the dyspnoea was much relieved.

Intravenous euphyllin was administered regularly every night, and always with the same beneficial effect. After a week it was possible to dispense with euphyllin which was thereafter only administered when necessary; perhaps once every four or five

days. The patient felt less distressed, had attacks of coughing only occasionally, and then of much shorter duration. The breath sounds were clearer, with less accompaniments. The Cheyne-Stokes respirations, which were so definite during sleep on previous occasions, still showed a periodicity but much less noticeable.

CASE 6: Cerebral haemorrhage. -- A man of 58 years in a very drowsy state as the result of a cerebral lesion, and showing a normal type of respiration, was given 0.48 g. euphyllin intravenously. The injection was followed by an increase in the depth of respiration, as showed by a stethograph record (Fig. 7).

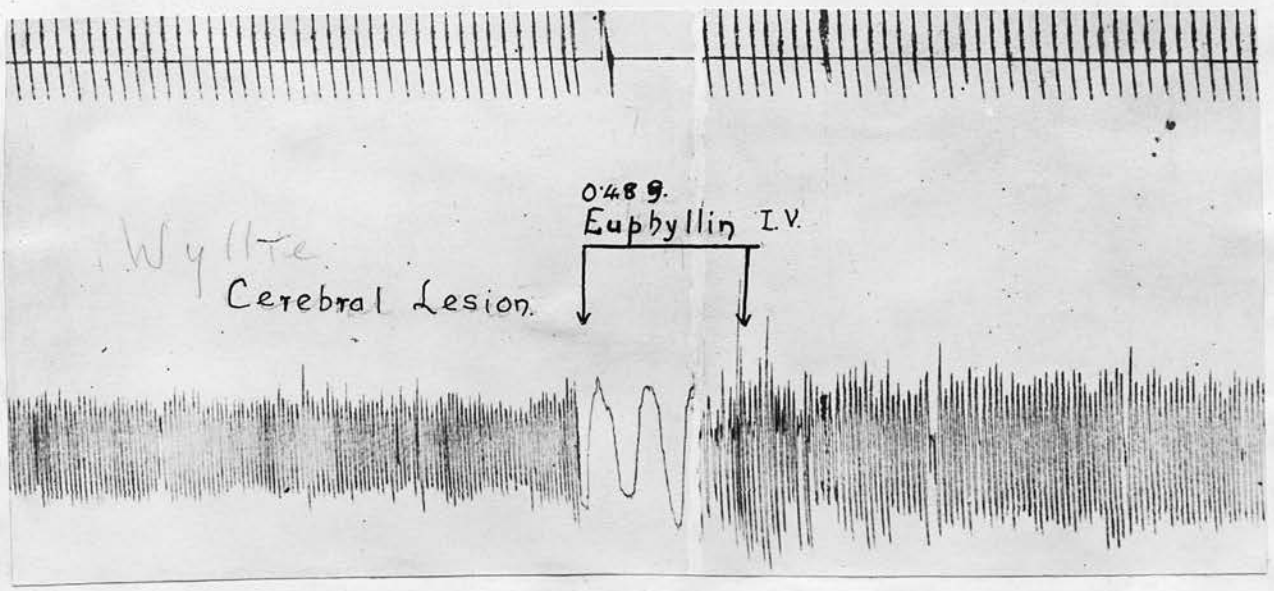

Fig. 7. The effect of euphyllin in increasing the depth of respiration of normal type.

CASE 7: Cessation of respiration after anaesthesia. A girl of 9 years, normal in all respects, with a sound cardiac muscle, had a tonsillectomy performed under ethyl chlorice and ether anaesthesia. The operation was completed and when the patient left the theatre the breathing was normal without periodicity, but ratherweak. After the patient was returned to bed, the respiration ceased altogether. Artificial respiration was performed but on stopping there was no sign of recommencing of the respiration. The administration of CO_2 was followed by a few deep gasps, but on removal of the CO_2 there was again a complete cessation of breathing. Thereupon 0.24 g. euphyllin was given intramuscularly, and the patient commenced breathing within half a minute after the injection. The breathing, however, again became shallower, and within five minutes after the first injection another 0.24 g. euphyllin was given intramuscularly. The respiration became deeper, and continued in a normal fashion.

These cases clearly show that euphyllin has a definite action in Cheyne-Stokes respiration as well as a stimulatory action on normal respiration. The question now arises as to the mode of action.

In looking for the principle which was most effective in the abolition of Cheyne-Stokes respiration, it was clearly shown (Cases 1, 2, and 4) that ethylenediamine had a marked stimulating effect with abolition of Cheyne-Stokes respiration, and that theophylline alone had no effect. It was shown though, that theophylline enhances the effect of ethylenediamine; that it intensifies the action and that it increases the time of duration. Further, as demonstrated in case 2, a single injection of the compound may be more effective than its two components given separately in succession.

Barbour and Hjort (1920) were the first to suggest that ethylenediamine stimulates respiration, although Piazza (1915) had clearly shown that the injection of other amines, for example, allyl amine, was followed by an acceleration of respiration. In the experiments of Barbour and Hjort there was in addition to the respiratory action, a fall in blood pressure which would be sufficient to account for the increased pulmonary ventilation, a fall of pressure in the carotid sinus producing this effect as shown by Heymans and others in 1933.

On account of the almost instantaneous action of the drug in Cheyne-Stokes breathing, and its ac-

tion in rousing comatose patients to wakefulness, Vogl (1932) holds that the mode of action of euphyllin is stimulation of the respiratory centre. Guggenheimer (1932, 1933) however, maintains that euphyllin produces an increased cardiac efficiency together with a coronary and cerebral vasodilatation. On account of this there is a proportional increase in the oxygen supply to the respiratory centre and counteraction of periodic breathing. This view is supported by Paul and others, who found that with the disappearance of the respiratory periodicity after the injection of euphyllin there was a fall in venous and intrathecal pressures, and they regarded this suggestive of an improvement in the cerebral circulation.

Greppi (1934) demonstrated a rapid drop in the cerebrospinal fluid pressure after the intravenous administration of euphyllin, and believed that this was most probably the result of an improved cerebral circulation. That a reduction of the cerebrospinal fluid pressure alone is apparently ineffective in abolishing Cheyne-Stokes respiration was shown by Greeve and Heeren, who failed to produce a change in the respiration after the administration of 50 per cent. glucose.

It is generally thought that the common underlying basis of Cheyne-Stokes respiration is a depression of the medullary respiratory centres. Oxygen lack, which has been shown by Smyth (1937) to depress the medullary respiratory centre, is probably the cause of the depression in cases of cardiovascular disease, such as described in the first six cases. On this assumption depression of the respiratory centre may be abolished by euphyllin by one or both of the two suggested mechanisms: (a) a direct stimulating action of the drug on the respiratory centre, independent of circulatory changes; (b) an increased circulation through the respiratory centre improving its oxygen supply.

(a) Direct stimulation of the respiratory centre would be expected to produce the following changes:-

(1) Increased pulmonary ventilation, with resulting lowering of the alveolar CO_2 content of arterial blood.

(2) Similar changes should be demonstrable on the normally acting respiratory centre as well as that depressed by oxygen lack. If euphyllin caused an increased blood flow through the normal respira-

tory centre, there would result a decreased rather than increased pulmonary ventilation (McMichael 1937). Hence an increased pulmonary ventilation in normal subjects would favour the view of direct stimulation of the centre.

That there is a definite increase in pulmonary ventilation was shown by McMichael (Marais and McMichael) who analysed the air collected in a Douglas bag before and after the administration of euphyllin in cases 1, 2 and 4, and in one normal subject (Table 1).

TABLE 1.

Euphyllin and Pulmonary ventilation

Subject	Before euphyllin		After 0.48 euphyllin intravenously		
	O_2 consump. (c.cm./min)	Vent equiv. CO_2	O_2 consump. (c.cm/min)	Vent equiv. CO_2	per cent change in pulm.vent
		Cheyne-Stokes breathing			
Case 4	247	6.32	258	7.20	14
Case 1	205	4.24	209	6.12	44
Case 2	272	3.92	310	4.20	9
		Normal			
J.M.	323	2.88	328	3.25	13

Consump.= Consumption; vent.equiv.CO_2 = ventilation equivalent for CO_2

In case 1 arterial punctures were also performed before and after giving euphyllin and the CO_2 content of the arterial blood estimated in a van Slyke apparatus. The blood taken during the Cheyne-Stokes phase was a mixed sample taken during apnoea and hyperpnoea.

Arterial CO_2 content in volumes per cent.

Before euphyllin (Cheyne-Stokes breathing)	After euphyllin (Normal breathing).
53.1	48.3

There is therefore a definite lowering of the CO_2 content of the arterial blood, which proves that euphyllin has a direct stimulating effect on the respiratory centre. In addition to these measurements the increase in amplitude of the respirations was shown graphically in case 6 (Fig. 8).

On account of the drowsy state of the patient the conscious influence of the injection on the respiration was at a minimum. The direct stimulating effect on the respiratory centre was shown in case 7 where CO_2 which is such a powerful respiratory stimulant, only produced a transient effect. Here the injection of euphyllin completely restored the normal respirations.

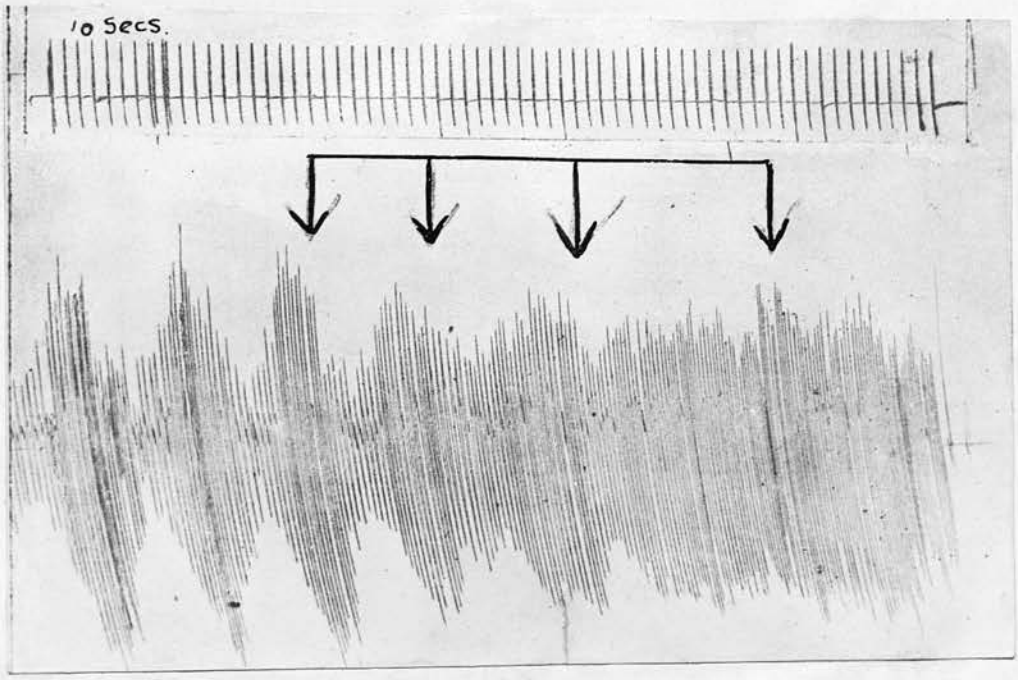

Fig. 8. At each arrow 0.1 g. euphyllin was injected intravenously. The periodicity becomes less pronounced with successive doses and finally disappears.

In order to find whether the stimulating effect of euphyllin on the respiratory centre is enhanced by an increased circulation through the brain as maintained by Guggenheimer, measurements of more important circulatory functions were made:-

1. Pulse rate. - In all cases this remained constant throughout the period of injection and after respiration was restored to normal.

2. Blood pressure. - There was no significant change in the blood pressure accompanying the euphyllin effect.

3. Electrocardiographic changes. - In case 1 continuous electrocardiographic records were made, before, during and after the injection. No changes were demonstrable in any of the complexes.

4. Cardiac output. - McMichael, using Grollman's acetylene method, and taking all the necessary precautions, measured the cardiac output before and after the injection of euphyllin in one cardiac subject (Case 4) and also in one normal case:-

TABLE 2.

Euphyllin and Cardiac Output.

	Before euphyllin			After euphyllin		
	A.V. O_2 diff. (c.cm./ litre)	O_2 consump. (c.cm./ min)	Cardiac output (litres/ min.)	A.V. O_2 diff. (c.cm./ litre)	O_2 consump (c.cm./ min.)	Cardiac output (Litres/ min.)
Case 4	149	247	1.66	157	258	1.64
Normal	60.5	323	5.33	62.5	328	5.25

A.V. = Arterio-venous

The results as shown in Table 2 clearly demonstrate that there is no significant change in the cardiac output, although the respiratory action, determined in the same experiment was quite striking in both cases. These figures indicate positively that the effect of euphyllin on normal and Cheyne-Stokes respiration occurs in the absence of any demonstrable change in the circulation as a whole.

Stewart and Jack measuring the cardiac output after the injection of euphyllin concluded that the response vary from patient to patient, and only in one case were they able to demonstrate an increase, while in some only a very transient increase was noticed; others showed no change at all, or even a fall.

The argument might be used that without changing the cardiac output or blood pressure, euphyllin causes a selective vasodilatation of the cerebral blood flow. Such an action would produce a diminished pulmonary ventilation in normal subjects, but as was clearly shown, there was an increase in the pulmonary ventilation. There is therefore, no reason to believe that euphyllin has any local effect on the cerebral circulation.

Cheyne-Stokes respiration is accompanied by

great subjective distress in most cases, and by interfering with the patient's rest and sleep it may prevent the improvement of the cardiac state, for as shown by Harrison and others it is during the onset of sleep that periodic breathing becomes most pronounced. Restoration of the normal respiratory rhythm may therefore ensure an easy night's rest.

The cases quoted prove beyond doubt that the intravenous injection of theophylline-ethylene-diamine in 0.48 g. doses arrests Cheyne-Stokes breathing, and that this effect is best procured by a slow administration of the drug. Half a cubic centimetre is injected as the respiratory movements begin to decline in amplitude; at the decline of the next period of hyperphoea a second 0.5 cm. and so on until the whole amount has been injected (Fig.8). The danger of giving the injection rapidly is that its powerful stimulating action on the respiratory centre may be superadded to the often intense dyspnoea of the hyperpnoeic phase (Fig. 8).

From the foregoing experiments one must conclude that the most striking action of euphyllin is the abolition of Cheyne-Stokes respiration, and

that while the active component responsible for this action is ethylenediamine, the combination of theophylline and ethylenediamine enhances the action and increases its potency. Further, the effect of euphyllin is produced by a direct stimulation of the medullary respiratory centres, and occurs in the absence of any demonstrable changes in the circulation.

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